REMARKS

Status of the Claims and Amendment

Claims 28-38 are all the claims pending in this application, and are rejected.

Response to Rejections Under 35 U.S.C. § 103(a)

Claims 28-38 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Cullis-Hill et al. (U.S. Patent No. 5,145,841) in view of Dictionary.com (2002, page 3) and Martindale: The Extra Pharmacopoeia 1996, page 11. The references are asserted for the same reasons set forth in the previous Office Action in addition to the following reasons.

First, although the Examiner acknowledges that Hill makes "no specific reference to the use of sodium salt of inulin sulfate", the Examiner asserts that because Hill teaches "a structurally close" sodium polysulfated xyloside (SP 54) that inhibits PMN elastase and other enzymes that degrade connective tissue and articular cartilage, one of ordinary skill in the art would have substituted sodium ion in the inulin polysulfate taught by Hill instead of trivalent metal ions.

Second, the Examiner asserts that Applicants' arguments and listing of drugs to show that some drugs used for treating osteoarthritis are not used for treating rheumatoid arthritis, is insufficient evidence to demonstrate that the treatments of osteoarthritis and rheumatoid arthritis are different. In this respect, the Examiner appears to assert that the drugs listed are different from the claimed inulin sulfate, and does not show that the claimed inulin sulfate can only be used to treat osteoarthritis. The Examiner asserts that according to Dictionary.com and

Martindale, both rheumatoid and osteoarthritis share common characteristics, i.e., both involve degradation of bone joints and are characterized by degradation/destruction of cartilage.

Furthermore, the Examiner asserts that Hill at column 12, lines 8-10 teaches "the compounds of his invention including inulin polysulfate" are useful for the treatment of rheumatoid arthritis and osteoarthritis. The Examiner appears to assert that Applicant's interpretation of Hill is incorrect because Hill at column 10, lines 50-53, teaches that the prior art, mentioned in the previous paragraph does not disclose the compounds and utility taught by Hill.

Third, with regard to Applicants' assertions that orally administered inulin polysulfate sodium salt has unexpectedly superior effectiveness compared to orally administered chondroitin sulfate at the same dose, the Examiner asserts that these effects are not unexpected as sodium salts of sulfated polysaccharides are known for the treatment of osteoarthritis. The Examiner asserts that it would have been routine for one of ordinary skill in the art to have looked for other more effective polysulfated polysaccharides, especially since inulin sulfate is suggested by Hill for the treatment of osteoarthritis and rheumatoid arthritis. The Examiner appears to assert that "[j]ust finding an agent that has better activity compared to another agent for the same method of treatment is not seen as an unexpected result", because one of ordinary skill in the art would not expect the activity of different polysulfated polysaccharides to be the same.

Applicants respectfully disagree for at least the following reasons in addition to those previously set forth.

With regard to the Examiner's first contention, Applicants note that the Examiner has failed to establish a *prima facie* case of obviousness because Hill in combination with Dictionary.com and Martindale do not teach or suggest each and every claim limitation of the claimed invention. M.P.E.P. § 2143. When evaluating claims for obviousness under 35 U.S.C. § 103, all the limitations of the claims must be considered and given weight.

In the present, case the Examiner has admitted that Hill makes "no specific reference to the use of sodium salt of inulin sulfate". Moreover, the Examiner has previously acknowledged that Hill does not exemplify the treatment of osteoarthritis using the claimed polysulphated polysaccharides. (See Office Action mailed October 27, 2008, page 8, lines 1-2).

Further, Hill does not teach nor suggest the use of the polysulphated polysaccharides by oral administration. In fact, Hill discloses that the preferred method of administration is by direct injection into the damaged tissues, such as for example, into the synovial cavity, and that when the compositions are used at high concentrations, then the compositions may be administered intra-muscularly, subcutaneously, intravenously or topically. See column 8, lines 51-59 of Hill.

Moreover, inulin is only mentioned once in Hill at column 5, line 57 in a laundry list of polysulphated polysaccharides with no further teaching or suggestion to guide one of ordinary skill in the art to selectively pick out inulin sulfate and modify it to a sodium salt as asserted by the Examiner. In fact, the compounds specifically identified by Hill to be effective polysulfated polysaccharides with anti-arthritic, anti-inflammatory activity for the treatment of rheumatoid arthritis, osteoarthritis, and inflammatory joint conditions are as follows.

> The *effective* polysuphated polysaccharides are believed to be those polysaccharides selected from the group consisting of dextran, xylan, chondroitin, dermatan and hyaluronic acid [emphasis added].

See column 9, lines 51-58 of Hill.

Also, Hill explicitly teaches that metallo complexes of such polysulphated polysaccharides enhance biological activity for the treatment of arthritis, rheumatism and inflammation. See Abstract , column 1, lines 9-10 and claim 1 at column 24 of Hill.. See Abstract , column 1, lines 9-10 and claim 1 at column 24 of Hill. Hill expressly states that:

> The present inventors have shown that because of the unusually strong affinity of the metal in these complexes of the invention for certain sulphate esters and oxygen atoms present on the carbohydrate rings of the polysaccharide, the metal alters the conformation and rigidity of the polymer chain thereby influencing its biological activity.

See column 10, lines 54-60 of Hill.

Accordingly, contrary to the Examiner's assertions that one of ordinary skill in the art would have been motivated to substitute trivalent metal ions for a sodium salt to produce sodium inulin sulfate because sodium polysulfated xyloside (SP 54) is "structurally close" to inulin sulfate, Hill explicitly teaches that:

> The effective complexes are those formed between the aforementioned polysulphated polysaccharides and multivalent ions, Ag+ and Au+, and quanternary ammonium compound complexes. The preferred polysaccharide is xylan polysulphate, ***most preferably SP54*** [emphasis added].

See column 9, lines 55-60 of Hill.

Furthermore, as previously argued, Hill teaches away from using polysulphated polysaccharides in the form of a salt of sodium, of potassium or of ammonium, because Hill states that "the metallo complexes of this class of drugs [polysulphated polysaccharides] were more potent stimulators of proteoglycan synthesis than the sodium salt" (see column 24, lines 1-

5 of Hill) and that "the formation of these metallo-polysulphated polysaccharide complexes provides a useful means of transporting selected metals into bodily tissues, since unlike the known salts of the polysulphated polysaccharides like *sodium, potassium*, or ammonium, which dissociate into the respective ions when dissolved in water, the complexes of the present invention do not dissociate in an aqueous or physiological media [emphasis added]" (see column 11, lines 49-59 of Hill).

Thus, even if one of ordinary skill in the art was somehow motivated to extrapolate the teachings of Hill to modify inulin sulfate, one of ordinary skill in the art would have been guided to modify inulin sulphate to a multivalent metallo complex of inulin sulfate and not a sodium ion as asserted by the Examiner.

With regard to the Examiner's second contention, Applicants note that contrary to the Examiner's assertions that both rheumatoid and osteoarthritis involve degradation of bone joints and are characterized by degradation/destruction of cartilage, osteoarthritis and rheumatoid arthritis are delineated in the medical art as separate, different diseases. In this respect, osteoarthritis is a degenerative joint disease characterized by "new bone formation" while rheumatoid arthritis is a systemic inflammatory disease with an immunological component characterized by "destruction of…bone" (see Martindale). Further, although articular cartilage damage occurs in osteoarthritis and rheumatoid arthritis, the cause of this damage in both diseases is different and underscores the etiological differences between the diseases. Specifically, the deterioration of the articular cartilage and overgrowth of bone in osteoarthritis is recognized to be due to "wear and tear", while the destruction of the articular cartilage (and

bone) is propagated by the inflammation of the joint connective tissue such as the synovial membranes. See Osteoarthritis vs. Rheumatoid Arthritis (submitted herewith). Further, Wieland et al., Nature Reviews Drug Discovery 4: 331-345 (2005) (submitted herewith) states that:

> Although OA is not a disease driven by inflammation, some degree of episodic, non-erosive synovial inflammation is common in OA, even during early states of the disease…in contrast to RA, synovial inflammation predominantly develops *secondarily to pathological processes in cartilage and bone* [emphasis added].

See page 336, paragraph bridging 1st and 2nd column of Wieland.

Thus, although OA and RA may involve some synovial inflammation, the underlying cause of OA is a different from that of RA, and the *etiological* treatment of OA is explicitly recognized in the art to differ from RA:

> In contrast to RA, no drugs are available with proven *disease-modifying efficacy* in OA [emphasis added].

See page 331, 2nd column, 1st sentence of last paragraph of Wieland.

Accordingly, one of ordinary skill in the art would have understood that medical treatment of osteoarthritis and rheumatoid arthritis would be directed to the underlying cause of the respective diseases. In the case of osteoarthritis, the treatment would be directed towards slowing the progression of articular cartilage loss and new bone formation that is the basis of osteoarthritis. On the other hand, the treatment of rheumatoid arthritis would be directed towards the inflammation of joint connective tissue that is the basis of rheumatoid arthritis. In this regard, the listing of drugs provided in the previous Amendment filed October 23, 2009 was for the purpose of emphasizing the differences between osteoarthritis and rheumatoid arthritis by the different way each is treated medically based upon the underlying cause.

With regard to the Examiner's third contention that orally administered inulin polysulfate sodium salt for the treatment of osteoarthritis is not unexpectedly superior to chondrotin sulfate sodium salt because sodium salts of sulfated polysaccharides are known for the treatment of osteoarthritis, and one of ordinary skill in the art would not expect the activity of different polysulfated polysaccharides to be the same, Applicants note that this appears to be in contrast to the Examiner's statement in the Office Action mailed October 27, 2008 (see bottom of page 8) that "[o]ne of skill in the art would expect the *structurally related polysulfated polysaccharides to perform the same functions* and would look for other related sulfated polysulfated polysaccharides for use in the method of treatments as instantly claimed [emphasis added]." In this respect, the Examiner is reminded that the Rule 132 Declaration was submitted for the purpose of demonstrating that it was not to be expected that all sulphated polysaccharides would have the same effectiveness for the treatment of osteoarthritis when administered orally. In this respect, the Rule 132 Declaration showed that the claimed inulin polysulphate sodium salt was unexpectedly superior for the treatment of osteoarthritis in comparison to chondroitin sulphate sodium salt at the same dose (see *in vivo* assay in Rule 132 Declaration submitted January 27, 2009).

Additionally, the Examiner is respectfully directed to Verbuggen et al., J. Rheumatol. 26: 1663-1671 (1999) (cited in the IDS submitted herewith) which is further evidence that one of ordinary skill in the art would not have expected that polysulphated polysaccharides may all be effective in the treatment of osteoarthritis. As explicitly stated at page 1670, 2nd paragraph of Verbuggen:

> In conclusion, it can be stated that the polysulfated polysaccharides xylosan polysulfate and chondroitin polysulfate, but not heparin, improved aggrecan synthesis by differentiated human articular cartilage cells in culture…These findings illustrate the repair-promoting effects of selected classes of sulfated polysaccharides [emphasis added].

Further, Verbuggen states at page 1670, 3rd paragraph that "[s]ulfated polysaccharides that positively affect cartilage metabolism could be classified among the structure modifying osteoarthritis drugs (SMOAD) and offer therapeutic benefits in the management of osteoarthritis". In addition, when improved aggrecan synthesis is observed, there were differences in this effect shown by each polysulphated polysaccharide disclosed in Verbuggen. Thus, Verbuggen explicitly teaches that some sulfated polysaccharides (for example heparin) do not have any effect in the treatment of osteoarthritis. Accordingly, it was not to be expected that all sulphated polysaccharides would have the same effectiveness for the treatment of osteoarthritis when administered orally.

However, *arguendo*, even if one of ordinary skill in the art was somehow inclined to look for other more effective polysulfated polysaccharides, as asserted by the Examiner, one of ordinary skill in the art would have been guided to the metallo complexes of the specific polysulphated polysaccharides identified by Hill at column 9, lines 51-58, which did not include inulin sulphate. One of ordinary skill in the art would not have even looked to the sodium salts of these polysulphated polysaccharides, since Hill found the sodium, potassium, and ammonium salts of these polysaccharides to have less biological activity than the metallo complexes.

Thus, the combination of Hill with Martindale and Dictionary.com do not teach or suggest the presently claimed method for treatment of osteoarthritis. Further, Hill in combination with Martindale and Dictionary.com would not have motivated one of ordinary skill

in the art at the time the application was filed to use polysulphated polysaccharides for the treatment of osteoarthritis. Moreover, one of ordinary skill in the art would not have been motivated to use the polysulphated polysaccharides in the form of a salt of sodium, potassium or ammonium.

Reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) is respectfully requested.

Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,

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